in 16% of LZ patients vs. 7% of controls. Forty-six percent of LZ patients vs. 13% of controls failed to achieve platelet engraftment. The cumulative incidence of engraftment of neutrophils plus platelets (using death without engraftment as the competing risk) was lower in the LZ group (54%) vs. the control group (83%) ($P = .005$). Day 100 survival rates were 58% for the LZ group vs. 92% for controls. Survival probability is shown in Figure 1.

Conclusions: LZ does not significantly affect time to neutrophil engraftment, but does appear to prolong time to platelet engraftment when compared to patients who did not receive LZ. LZ should be used cautiously early after stem cell transplantation.

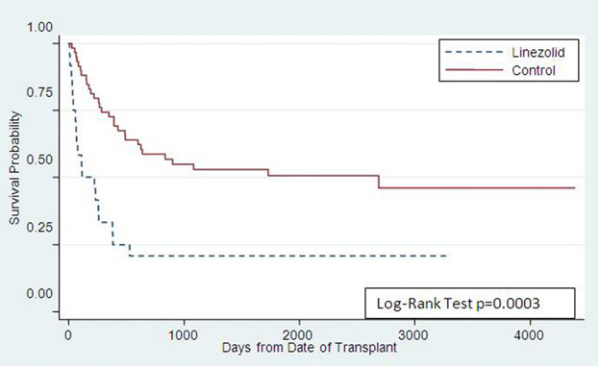

Figure 1. Overall Survival

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Association Between Mycophenolic Acid (MPA) Total Serum Trough Levels and Toxicity and Efficacy Outcomes in Cord Blood Transplantation (CBT) Recipients

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Background: Mycophenolate mofetil (MMF) is frequently combined with cyclosporine-A as immunosuppression in unrelated donor CBT. Recent evidence suggests that therapeutic drug monitoring of mycophenolic acid (MPA), the active metabolite of MMF, is advisable based on intra- and inter-patient variability of MMF pharmacokinetics (PK). Moreover, an increased incidence of acute graft-versus-host disease (aGVHD) has been associated with low unbound MPA AUCs in adult allograft recipients. This is highly relevant in CBT as aGVHD is a leading cause of transplant-related mortality. However, as AUCs are cumbersome, a limited PK parameter such as MPA troughs would be ideal. Also, the toxicity associated with MPA trough levels is not established.

Methods: We evaluated the association between serial MPA total serum trough levels in weeks 1-6 and transplant outcomes in pediatric and adult double-unit CB recipients transplanted 8/2009 to 6/2012 for hematologic malignancies with 4-6/6 HLA-A,B antigen, DRB1 allele matched CB grafts. To evaluate the association between trough levels and outcomes, the trough levels were dichotomized into < 2 mcg/mL and ≥ 2 mcg/mL for toxicity (delayed engraftment, gastrointestinal toxicity, viral infection), and < 0.5 mcg/mL and ≥ 0.5 mcg/mL for efficacy (aGVHD prevention) at each time point.

Results: Seventy-four patients had MPA total serum trough levels drawn weekly for 6 weeks. Sixty-one (82%) received myeloablative (MA) conditioning and 31 (42%) were CMV seropositive. Median trough levels by week were 0.9, 0.9, 0.6, 0.7, 0.9, and 1.3 mcg/mL. The change in trough levels over time did not reach significance ($P = .07$). Recipients of MA conditioning had lower MPA troughs than those who received non-myeloablative conditioning ($P = .03$). By time-dependent Cox regression analysis, there was no association between trough levels and toxicity as measured by time to neutrophil and platelet recovery or duration of total parenteral nutrition (TPN) in myeloablative CBT recipients, or time to viremia in CMV seropositive patients (Table 1A). In a competing risk 2-week landmark analysis, while differences between groups did not reach significance, it was notable that the incidence of severe (grade III-IV) aGVHD was more than doubled in those with a mean week 1 and 2 trough level < 0.5 mcg/mL (Table 1B).

Conclusions: Analysis of this limited patient population suggests that while MPA total serum trough levels appear to have little effect on toxicity outcomes, the early post-transplant (week 1-2) mean levels could be associated with the risk of severe (grade III-IV) aGVHD. Further investigation in a larger patient series is warranted.

Table
Association between MPA total serum trough levels and toxicity and efficacy outcomes

1A) Toxicity outcome: Time-dependent Cox regression

Outcome	N	HR (95% CI)	*P*-value
Time to neutrophils ≥ 0.5 k/mcL	61	1.45 (0.65 - 3.25)	0.36
Time to platelets ≥ 20 k/mcL	61	1.88 (0.82 - 4.30)	0.14
Time to TPN cessation	61	0.56 (0.20 - 1.58)	0.28
Time to CMV viremia	31	1.71 (0.38 - 7.59)	0.48

IB) Efficacy outcome: Cumulative incidence of aGVHD by day 100

Outcome	N	Cumulative incidence (95% CI)	*P*-value
aGVHD II-IV			
Trough < 0.5 mcg/mL	15	0.67 (0.41 - 0.92)	0.29
Trough ≥ 0.5 mcg/mL	57	0.57(0.44 - 0.71)	
aGVHD III-IV			
Trough < 0.5 mcg/mL	15	0.27 (0.03 - 0.50)	0.12
Trough < 0.5 mcg/mL	57	0.11 (0.03 - 0.19)	

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Incidence of Fluoride Toxicity in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Patients Taking Voriconazole

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